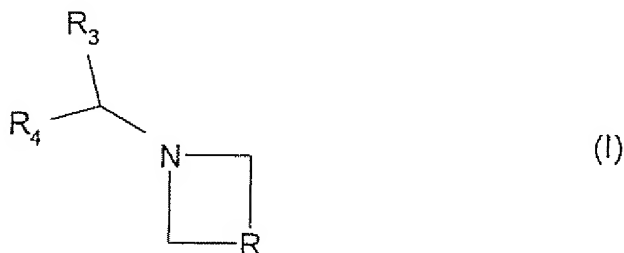


Amendment Pursuant to 37 C.F.R. § 1.121

IN THE CLAIMS:

The claims set forth below with amendments as indicated will replace all prior versions and listing of claims in the application.

1. (original) A combination comprising one or more products which activate dopaminergic neurotransmission in the brain and of one or more CB1 antagonist azetidine derivatives of formula I:



wherein

either A:

R is CR_1R_2 , $\text{C}=\text{C}(\text{R}_5)\text{SO}_2\text{R}_6$ or $\text{C}=\text{C}(\text{R}_7)\text{SO}_2\text{alk}$; wherein

either R_1 is hydrogen and R_2 is $-\text{C}(\text{R}_8)(\text{R}_9)(\text{R}_{10})$, $-\text{C}(\text{R}_8)(\text{R}_{11})(\text{R}_{12})$, $-\text{CO}-\text{NR}_{13}\text{R}_{14}$, $-\text{CH}_2-\text{CO}-\text{NR}_{13}\text{R}_{14}$, $-\text{CH}_2-\text{CO}-\text{R}_6$, $-\text{CO}-\text{R}_6$, $-\text{CO}-\text{cycloalkyl}$, $-\text{SO}-\text{R}_6$, $-\text{SO}_2-\text{R}_6$, $-\text{C}(\text{OH})(\text{R}_{12})(\text{R}_6)$, $-\text{C}(\text{OH})(\text{R}_6)(\text{alkyl})$, $-\text{C}(=\text{NOalk})\text{R}_6$, $-\text{C}(=\text{NO}-\text{CH}_2-\text{CH}=\text{CH}_2)\text{R}_6$, $-\text{CH}_2-\text{CH}(\text{R}_6)\text{NR}_{31}\text{R}_{32}$, $-\text{CH}_2-\text{C}(=\text{NOalk})\text{R}_6$, $-\text{CH}(\text{R}_6)\text{NR}_{31}\text{R}_{32}$, $-\text{CH}(\text{R}_6)\text{NHSO}_2\text{alk}$, $-\text{CH}(\text{R}_6)\text{NHCONHalk}$ or $-\text{CH}(\text{R}_6)\text{NHCOalk}$; or

R_1 is alkyl, $\text{NH}-\text{R}_{15}$, cyano, $-\text{S}-\text{alk}-\text{NR}_{16}\text{R}_{17}$, $-\text{CH}_2-\text{NR}_{18}\text{R}_{19}$ or $-\text{NR}_{20}\text{R}_{21}$;
and

R_2 is $-\text{C}(\text{R}_8)(\text{R}_{11})(\text{R}_{12})$;

R_3 and R_4 , which are identical or different, independently are either alkyl, cycloalkyl, aryl chosen from phenyl, naphthyl or indenyl, wherein aryl being unsubstituted or substituted by one or more halogen, alkyl, alkoxy,

formyl, hydroxyl, trifluoromethyl, trifluoromethoxy, -CO-alk, cyano, -COOH, -COOalk, -CONR₂₂R₂₃, -CO-NH-NR₂₄R₂₅, alkylsulfanyl, alkylsulfinyl, alkylsulfonyl, alkylsulfanylalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, hydroxyalkyl or -alk-NR₂₄R₂₅; or heteroaryl chosen from benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, 2,3-dihydroxybenzofuryl, 2,3-dihydrobenzothienyl, furyl, imidazolyl, isochromanyl, isoquinolyl, pyrrolyl, pyridyl, pyrimidinyl, quinolyl, 1,2,3,4-tetrahydroisoquinolyl, thiazolyl and thienyl, wherein heteroaryl is unsubstituted or substituted by one or more halogen, alkyl, alkoxy, hydroxyl, trifluoromethyl, trifluoromethoxy, cyano, -COOH, -COOalk, -CO-NH-NR₂₄R₂₅, -CONR₂₂R₂₃, -alk-NR₂₄R₂₅, alkylsulfanyl, alkylsulfinyl, alkylsulfonyl, alkylsulfanylalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl or hydroxyalkyl;

R₅ is hydrogen or alkyl;

R₆ is Ar₁ or Het₁;

R₇ is cycloalkyl, heterocycloalkyl or heterocyclenyl optionally substituted by -CSO-phenyl;

R₈ is hydrogen or alkyl;

R₉ is -CO-NR₂₆R₂₇, -COOH, -COOalk, -CH₂OH, -NH-CO-NH-alk, -CH₂-NHR₂₈ or -NHCOOalk;

R₁₀ is Ar₁ or Het₁;

R₁₁ is -SO₂-alk, -SO₂-Ar₁ or -SO₂-Het₁;

R₁₂ is hydrogen, Ar₁ or Het₁;

R₁₃ is hydrogen or alkyl;

R₁₄ is Ar₁, Het₁, -alk-Ar₁ or -alk-Het₁;

R₁₅ is alkyl, cycloalkyl or -alk-NR₂₉R₃₀;

R₁₆ and R₁₇, which are identical or different, independently are either hydrogen or alkyl; or

R₁₆ and R₁₇ taken together with the nitrogen atom to which they are attached form a saturated or unsaturated 3 to 10 ring membered mono- or 5 to 10 ring membered bicyclic heterocycle, optionally comprising one or more other heteroatoms chosen from oxygen, sulfur and nitrogen and optionally substituted by one or more alkyl;

R₁₈ is hydrogen or alkyl;

R₁₉ is hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, cycloalkylcarbonyl, -SO₂alk, -CO-NHalk or -COOalk; or

R₁₈ and R₁₉ taken with the nitrogen atom to which they are attached form a saturated or unsaturated 3 to 10 ring membered mono- or 5 to 10 ring membered bicyclic heterocycle, optionally comprising one or more heteroatoms chosen from oxygen, sulfur and nitrogen and optionally substituted by one or more alkyl;

-NR₂₀R₂₁ is a saturated or unsaturated monocyclic heterocycle having 3 to 8 ring members and optionally comprising another heteroatom chosen from oxygen, nitrogen and sulfur;

R₂₂ and R₂₃, which are identical or different, independently are hydrogen or alkyl;
or

R₂₂ and R₂₃ taken together with the nitrogen atom to which they are attached form a saturated mono- or bicyclic heterocycle having 3 to 10 ring members optionally comprising another heteroatom chosen from oxygen, sulfur and nitrogen and optionally being substituted by one more alkyl;

R₂₄ and R₂₅, which are identical or different, independently are hydrogen, alkyl, -COOalk, cycloalkyl, alkylcycloalkyl, -alk-O-alk or hydroxyalkyl; or

R₂₄ and R₂₅ taken together with the nitrogen atom to which they are attached form a saturated or unsaturated and mono- or bicyclic heterocycle having 3 to 10 ring members optionally comprising another heteroatom chosen from oxygen, sulfur and nitrogen and optionally being substituted by one or

more alkyl, -COalk, -COOalk, -CO-NHalk, -CS-NHalk, oxo,
hydroxyalkyl, -alk-O-alk or -CO-NH₂;

R₂₆ and R₂₇, which are identical or different, independently are hydrogen, alkyl,
hydroxyalkyl, cycloalkyl, cycloalkylalkyl, -alk-COOalk, -alk-Ar₁, alk-Het₁,
Het₁ or -alk-N(alk)₂; or

R₂₆ and R₂₇ taken together with the nitrogen atom to which they are attached form
a saturated or unsaturated and mono- or bicyclic heterocycle having 3 to
10 ring members and optionally comprising one or more heteroatoms
chosen from oxygen, sulfur and nitrogen and optionally substituted by one
or more alkyl, alkoxy or halogen;

R₂₈ is -CH₂-alk, benzyl, -SO₂alk, -CONHalk, -COalk, cycloalkylalkylcarbonyl,
cycloalkylcarbonyl or -CO-(CH₂)_nOH, wherein n is an integer from 1 to 3;

R₂₉ and R₃₀, which are identical or different, independently are hydrogen or alkyl;
or

R₂₉ and R₃₀ taken together with the nitrogen atom to which they are attached form
a saturated mono- or bicyclic heterocycle having 3 to 10 ring members
optionally comprising another heteroatom chosen from oxygen, sulfur and
nitrogen and optionally being substituted by one or more alkyl radicals;

R₃₁ and R₃₂, which are identical or different, independently are hydrogen, alkyl,
Ar₁ or -alk-Ar₁; or

R₃₁ and R₃₂ taken together with the nitrogen atom to which they are attached form
a heterocycle chosen from aziridinyl, azetidiny, pyrrolidinyl and
piperidinyl;

Ar₁ is phenyl or naphthyl optionally substituted by one or more substituents
chosen from halogen, alkyl, alkoxy, -CO-alk, cyano, -COOH, -COOalk,
-CONR₂₂R₂₃, -CO-NH-NR₂₄R₂₅, alkylsulfanyl, alkylsulfinyl,
alkylsulfonyl, alkylsulfanylalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl,
hydroxyalkyl, -alk-NR₂₄R₂₅, -NR₂₄R₂₅, alkylthioalkyl, formyl, hydroxyl,
CF₃, OCF₃, Het₁, O-alk-NH-cycloalkyl or SO₂NH₂;

Het₁ is a saturated or unsaturated and mono- or bicyclic heterocycle having 3 to 10 ring members and comprising one or more heteroatoms chosen from oxygen, sulfur and nitrogen and optionally substituted by one or more halogen, alkyl, alkoxy, alkoxycarbonyl, -CONR₂₂R₂₃, hydroxyl, hydroxyalkyl, oxo or SO₂NH₂;

or B: wherein

R is CHR₃₃; wherein

R₃₃ is -NHCOR₃₄ or -N(R₃₅)-Y-R₃₆;

Y is CO or SO₂;

R₃ and R₄, which are identical or different, are either aryl chosen from phenyl, naphthyl and indenyl, wherein aryl being unsubstituted or substituted by one or more halogen, alkyl, alkoxy, formyl, hydroxyl, trifluoromethyl, trifluoromethoxy, -CO-alk, cyano, -COOH, -COOalk, -CONR₃₇R₃₈, -CO-NH-NR₃₉R₄₀, alkylsulfanyl, alkylsulfinyl, alkylsulfonyl, alkylsulfanylalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, hydroxyalkyl or -alk-NR₃₇R₃₈; or heteroaryl chosen from benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, 2,3-dihydro-benzofuryl, 2,3-dihydro-benzothienyl, pyrimidinyl, furyl, imidazolyl, isochromanyl, isoquinolyl, pyrrolyl, pyridyl, quinolyl, 1,2,3,4-tetrahydroisoquinolyl, thiazolyl and thienyl, wherein heteroaryl being unsubstituted or substituted by halogen, alkyl, alkoxy, hydroxyl, trifluoromethyl, trifluoromethoxy, cyano, -COOH, -COOalk, -CO-NH-NR₃₉R₄₀, -CONR₃₇R₃₈, -alk-NR₃₉R₄₀, alkylsulfanyl, alkylsulfinyl, alkylsulfonyl, alkylsulfanylalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl or hydroxyalkyl;

R₃₄ is -alk-SO₂-R₄₁, -alk-SO₂-CH=CH-R₄₁, Het₂ substituted by -SO₂-R₄₁ or phenyl substituted by -SO₂-R₄₁ or -alk-SO₂-R₄₁;

R₃₅ is hydrogen or alkyl;

R₃₆ is phenylalkyl, Het₂ or Ar₂;

R₃₇ and R₃₈, which are identical or different, independently are hydrogen or alkyl;
or

R₃₇ and R₃₈ taken together with the nitrogen atom to which they are attached form a saturated mono- or bicyclic heterocycle having 3 to 10 ring members optionally comprising another heteroatom chosen from oxygen, sulfur and nitrogen and optionally being substituted by one or more alkyl;

R₃₉ and R₄₀, which are identical or different, independently are hydrogen or alkyl, -COOalk, cycloalkyl, alkylcycloalkyl, -alk-O-alk or hydroxyalkyl; or

R₃₉ and R₄₀ taken together with the nitrogen atom to which they are attached form a saturated or unsaturated and mono- or bicyclic heterocycle having 3 to 10 ring members optionally comprising another heteroatom chosen from oxygen, sulfur and nitrogen and optionally being substituted by one or more alkyl, -COalk, -COOalk, -CO-NHalk, -CS-NHalk, oxo, hydroxyalkyl, -alk-O-alk or -CO-NH₂;

R₄₁ is alkyl, Ar₂ or Het₂;

Ar₂ is phenyl, naphthyl or indenyl radical, these radicals optionally being substituted by one or more halogen, alkyl, alkoxy, cyano, -CO-alk, -COOH, -COOalk, -CONR₄₂R₄₃, -CO-NH-NR₄₄R₄₅, alkylsulfanyl, alkylsulfinyl, alkylsulfonyl, -alk-NR₄₄R₄₅, -NR₄₄R₄₅, alkylthioalkyl, formyl, hydroxyl, hydroxyalkyl, Het₂, -O-alk-NH-cycloalkyl, OCF₃, CF₃, -NH-CO-alk, -SO₂NH₂, -HN-COCH₃, -NH-COOalk or Het₂ or else on two adjacent carbon atoms by a dioxymethylene;

Het₂ is a saturated or unsaturated and mono- or bicyclic heterocycle having 3 to 10 ring members and comprising one or more heteroatoms chosen from oxygen, sulfur and nitrogen optionally substituted by one or more alkyl, alkoxy, vinyl, halogen, alkoxycarbonyl, oxo, hydroxyl, OCF₃ or CF₃, the nitrogenous heterocycles optionally being in their N-oxidized form;

R₄₂ and R₄₃, which are identical or different, independently are hydrogen or alkyl;
or

R₄₂ and R₄₃ taken together with the nitrogen atom to which they are attached form a saturated mono- or bicyclic heterocycle having 3 to 10 ring members optionally comprising another heteroatom chosen from oxygen, sulfur and nitrogen and optionally being substituted by one or more alkyl;

R₄₄ and R₄₅, which are identical or different, independently are hydrogen, alkyl, -COOalk, cycloalkyl, alkylcycloalkyl, -alk-O-alk or hydroxyalkyl; or

R₄₄ and R₄₅ taken together with the nitrogen atom to which they are attached form a saturated or unsaturated and mono- or bicyclic heterocycle having 3 to 10 ring members optionally comprising another heteroatom chosen from oxygen, sulfur and nitrogen and optionally being substituted by one or more alkyl, -COalk, -COOalk, -CO-NHalk, -CS-NHalk, oxo, hydroxyalkyl, -alk-O-alk or -CO-NH₂;

or C: wherein

R is CHR₄₆, wherein

R₄₆ is -N(R₄₇)R₄₈, -N(R₄₇)-CO-R₄₈ or -N(R₄₇)-SO₂R₄₉;

R₃ and R₄, which are identical or different, represent either an aryl chosen from phenyl, naphthyl and indenyl, wherein aryl being unsubstituted or substituted by one or more halogen, alkyl, alkoxy, formyl, hydroxyl, trifluoromethyl, trifluoromethoxy, -CO-alk, cyano, -COOH, -COOalk, -CONR₅₀R₅₁, -CO-NH-NR₅₂R₅₃, alkylsulfanyl, alkylsulfinyl, alkylsulfonyl, alkylsulfanylalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, hydroxyalkyl or -alk-NR₇R₈; or a heteroaryl chosen from benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, 2,3-dihydrobenzofuryl, 2,3-dihydrobenzothienyl, furyl, imidazolyl, isochromanyl, isoquinolyl, pyrrolyl, pyridyl, pyrimidyl, quinolyl, 1,2,3,4-tetrahydroisoquinolyl, thiazolyl and thienyl, wherein heteroaryl being unsubstituted or substituted by halogen, alkyl, alkoxy, hydroxyl, trifluoromethyl, trifluoromethoxy, cyano, -COOH, -COOalk, -CO-NH-NR₅₂R₅₃, -CONR₅₀R₅₁, -alk-NR₅₂R₅₃, alkylsulfanyl,

alkylsulfinyl, alkylsulfonyl, alkylsulfanylalkyl, alkylsulfinylalkyl,
alkylsulfonylalkyl or hydroxyalkyl;

R₄₇ is -C(R₅₄)(R₅₅)-Het₃, Het₃, -C(R₅₄)(R₅₅)-Ar₃, Ar₃, cycloalkyl or norbornyl;

R₄₈ is hydrogen or hydroxyalkyl, -alk-COOalk, -alk-CONR₅₀R₅₁, -alk-NR₅₀R₅₁,
alkoxy; Ar₃, Het₃, -CH₂Ar₃, -CH₂Het₃ or alkyl, optionally substituted with
one or more halogen;

R₄₉ is hydroxyalkyl, -alk-COOalk, -alk-CONR₅₀R₅₁, -alk-NR₅₀R₅₁, alkoxy, Ar₃,
Het₃, -CH₂Ar₃, -CH₂Het₃ or alkyl optionally substituted with one or more
halogen;

R₅₀ and R₅₁, which are identical or different, independently are hydrogen or alkyl;
or

R₅₀ and R₅₁ taken together with the nitrogen atom to which they are attached form
a saturated mono- or bicyclic heterocycle having 3 to 10 ring members
optionally comprising another heteroatom chosen from oxygen, sulfur and
nitrogen and optionally being substituted by one or more alkyl;

R₅₂ and R₅₃, which are identical or different, independently are hydrogen or alkyl,
-COOalk, cycloalkyl, alkylcycloalkyl, -alk-O-alk or hydroxyalkyl; or

R₅₂ and R₅₃ taken together with the nitrogen atom to which they are attached form
a saturated or unsaturated and mono- or bicyclic heterocycle having 3 to
10 ring members optionally comprising another heteroatom chosen from
oxygen, sulfur and nitrogen and optionally being substituted by one or
more alkyl, -COalk, -COOalk, -CO-NHalk, -CS-NHalk, oxo,
hydroxyalkyl, -alk-O-alk or -CO-NH₂;

R₅₄ is hydrogen, hydroxyalkyl, -alk-COOalk, -alk-CONR₅₀R₅₁, -alk-NR₅₀R₅₁,
alkoxyalkyl, Ar₃, Het₃, -CH₂Ar₃, -CH₂Het₃ or alkyl optionally substituted
with one or more halogen;

R₅₅ is hydrogen or hydroxyalkyl, -alk-COOalk, -alk-CONR₅₀R₅₁, -alk-NR₅₀R₅₁,
alkoxyalkyl or alkyl optionally substituted with one or more halogen; or

R₅₄ and R₅₅ taken together with the carbon atom to which they are attached form a saturated mono- or bicyclic ring having 3 to 10 ring members optionally comprising another heteroatom chosen from oxygen, sulfur and nitrogen and optionally being substituted by one or more alkyl;

Ar₃ is phenyl, naphthyl or indenyl, optionally being substituted by one or more halogen, alkyl, alkoxy, -CO-alk, cyano, -COOH, -COOalk, -CONR₅₆R₅₇, -CO-NH-NR₅₈R₅₉, alkylsulfanyl, alkylsulfinyl, alkylsulfonyl, -alk-NR₅₈R₅₉, -NR₅₈R₅₉, alkylthioalkyl, formyl, CF₃, OCF₃, Het₃, -O-alk-NH-cycloalkyl, SO₂NH₂, hydroxyl, hydroxyalkyl, -NHCOalk or -NHCOOalk or on 2 adjacent carbon atoms by dioxymethylene;

Het₃ is a saturated or unsaturated and mono- or bicyclic heterocycle having 3 to 10 ring members and comprising one or more heteroatoms chosen from oxygen, sulfur and nitrogen optionally substituted by one or more alkyl, alkoxy, halogen, alkoxycarbonyl, oxo or hydroxyl, the nitrogenous heterocycles optionally being in their N-oxidized form;

R₅₆ and R₅₇, which are identical or different, independently are hydrogen or alkyl radical; or

R₅₆ and R₅₇ taken together with the nitrogen atom to which they are attached form a saturated mono- or bicyclic heterocycle having 3 to 10 ring members optionally comprising another heteroatom chosen from oxygen, sulfur and nitrogen and optionally being substituted by one or more alkyl;

R₅₈ and R₅₉, which are identical or different, independently are hydrogen or alkyl; or

R₅₈ and R₅₉ taken together with the nitrogen atom to which they are attached form a saturated mono- or bicyclic heterocycle having 3 to 10 ring members optionally comprising another heteroatom chosen from oxygen, sulfur and nitrogen and optionally being substituted by one or more alkyl;

alk is an alkyl or alkylene radical; and wherein

the alkyl, alkylene and alkoxy radicals have straight or branched chains and comprise 1 to 6 carbon atoms, the cycloalkyl radicals comprise 3 to 10 carbon atoms and the heterocycloalkyl and heterocyclenyl radicals comprise 3 to 10 carbon atoms; or
an optical isomer thereof or a pharmaceutically acceptable salt thereof.

2. (original) The combination according to claim 1, wherein the compound of formula (I) is chosen from the following compounds:
N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(pyrid-3-yl)methylsulfonamide
or
N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(3,5-difluorophenyl)methylsulfonamide, or a
pharmaceutically acceptable salt thereof.
3. - 9. (canceled)
10. (currently amended) The combination according to claim 1, ~~characterized in that~~
wherein the product which activates dopaminergic neurotransmission in the brain is levodopa and the CB1 antagonist is N-{1-[bis(4-chloro-phenyl)methyl]azetidin-3-yl}-N-(3,5-difluorophenyl)-methylsulfonamide.
11. - 19. (canceled)
20. (original) A pharmaceutical composition comprising one or more products which activate dopaminergic neurotransmission in the brain and one or more CB1 antagonists of formula (I) as defined in claim 1 in combination with a compatible and pharmaceutically acceptable vehicle.
21. (original) The pharmaceutical composition according to claim 20, wherein the compound of formula (I) as defined in claim 1 is chosen from the following compounds:
N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(pyrid-3-yl)methylsulfonamide, or

N-{ 1-[bis(4-chlorophenyl)methyl]azetidin-3-yl }-N-(3,5-difluorophenyl)methylsulfonamide, or a pharmaceutically acceptable salt thereof.

22. - 28. (canceled)

29. (original) The pharmaceutical composition according to claim 20, wherein the product which activates dopaminergic neurotransmission in the brain is levodopa and the CB1 antagonist is N-{ 1-[bis(4-chlorophenyl)methyl]azetidin-3-yl }-N-(3,5-difluorophenyl)methylsulfonamide.

30. - 34. (canceled)

35. (original) The pharmaceutical composition according to claim 20 for a simultaneous use, separate use or use spread out over time.

36. (original) The pharmaceutical composition according to claim 20 wherein the CB1 antagonist of formula (I) as defined in claim 1 is present in an amount of from about 0.1 mg to about 500 mg.